Novel Insights from Clinical Practice

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22q13 Microduplication Syndrome in Siblings with Mild Clinical Phenotype: Broadening the Clinical and Behavioral Spectrum

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Established Facts

- Terminal deletion of chromosome 22q is a rare disorder with variable degree of developmental delay and association of morphological symptoms. It may arise as a de novo event or, less frequently, from parental balanced reciprocal translocation or a pericentric inversion of chromosome 22.
- Involvement of *SHANK3* in the duplicated segment is crucial in the emerging neurobehavioral phenotype.

Novel Insights

- Familial reoccurence presented in this paper is extremely rarely reported.
- Our patients have unusually mild clinical symptoms – they share very similar morphological features, neither patient has microcephaly, they both have borderline intellect, and they have the exact same chromosomal breakpoints on array CGH.
- *SHANK3* is involved in the microduplication, and the mother is a carrier of a pericentric inversion of chromosome 22.

Keywords
Array CGH · Distal trisomy 22q · Pericentric inversion · 22qter · 22q13

Abstract
Distal duplication 22q (22q13.3qter) is a rare condition with only 24 cases described so far. Parental balanced reciprocal translocations and pericentric inversions involving chromosome 22 predispose to the conception of an unbalanced offspring and are more frequently reported than de novo events. The clinical phenotype of patients is highly variable and does not necessarily correlate with the extent of the duplicated segment. Short stature, microcephaly, hypertelorism, cleft lip or palate, low-set ears, and intellectual disability seem to be the most consistent features. Familial reoccurrence is extremely rarely reported. Here, we report 2 siblings with a 22q13.3qter duplication detected by array

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CGH; their mother is a carrier of a pericentric inversion in chromosome 22. Their relatively mild phenotype and identical chromosomal breakpoints as well as duplication size are unique. This is the first case described so far.

Duplication of the distal long arm of chromosome 22 (22q13qter) is a rare cytogenetic anomaly, resulting in variable degrees of developmental delay and dysmorphism with or without obvious neuropsychiatric symptoms in the affected individuals. To date, only 24 cases have been published, the majority of which were identified by conventional cytogenetics and FISH [Fryns et al., 1980; Schinzel, 1981; Bendel et al., 1982; Biesecker et al., 1995; Wieczorek et al., 1998; Petek et al., 2000; Boyd et al., 2005; Hou, 2005; Feenstra et al., 2006; Failla et al., 2007; Okamoto et al., 2007; Peeters et al., 2008; Wu et al., 2010; Jafri et al., 2011; Han et al., 2013; Ahn et al., 2014; Magri et al., 2015; Chen et al., 2017; Johannessen et al., 2019]. Two of the above patients were identified in the context of large studies designed for unexplained developmental delay and schizophrenia with limited phenotype description [Wu et al., 2010; Ahn et al., 2014]. Han et al. [2013] reported the 2 smallest duplications of 22q13 so far.

The molecular cytogenetic classification of pure distal 22q duplications was proposed by Feenstra et al. [2006] distinguishing 4 groups: large duplication (22q12qter), intermediate (22q13.1qter), small (22q13.2qter), and smallest duplication (22q13.3qter). They also provided an overview of patients from the literature and their own cases. They concluded that patients having a duplication extending from 22q13 to qter show most clinical problems and have a lower survival rate, but even patients with assumingly comparable duplications show great variations, and comparison between them is difficult. The most consistent features are pre-and postnatal growth retardation, cleft palate with or without cleft lip, micrognathia, microcephaly, hypertelorism, low-set ears, congenital heart defect, renal and genital anomalies as well as hypotonia. In some cases, decreased life expectancy is reported [Feenstra et al., 2006].

The majority of cases arise from parental balanced translocations, a smaller proportion of patients are de novo, or the offspring of a parent carries a pericentric inversion or insertion in chromosome 22. Jafri et al. [2011] demonstrated that during homologous recombination, commonly occurring in the process of meiosis, a parent with an inverted chromosome 22 has likelihood to produce a gamete with a rearranged form of the inverted chromosome 22. This rearranged form already contains either a deletion or duplication, resulting in the conception of an unbalanced offspring after fertilization [Jafri et al., 2011].

Magri et al. [2015] assessed the clinical and cytogenetic/molecular cytogenetic properties of 10 patients with duplications distal from 22q13 – the intermediate, small, and smallest terminal duplications – and explained the possible molecular mechanism involving a break-induced replication as part of a nonreciprocal translocation event, leading to a de novo unbalanced translocation of the distal part of chromosome 22. They also pointed out that patients with apparently the same duplicated region show a wide spectrum of phenotypic variations; part of these differences may be due to the different genetic background in which the duplications arise, but also to the different resolution of methods used to evaluate the extent of duplications [Magri et al., 2015]. The 6 patients with a molecular characterization of the breakpoints and array CGH analysis are those reported by Failla et al. [2007], Okamoto et al. [2007], Peeters et al. [2008], Magri et al. [2015], Chen et al. [2017], and Johannessen et al. [2019].

Here, we present 2 siblings with a rare 22q13qter duplication and only mild symptoms, detected by array CGH and FISH, whose mother is a carrier of a pericentric inversion of chromosome 22.

Case Presentations and Results

Patient 1

Patient 1 was born at term as the 3rd child of healthy, nonconsanguineous Caucasian parents, with normal weight (2,750 g; 10th percentile) and length (49 cm; 25th percentile); occipitofrontal circumference (OFC) was not recorded. The mother and father are both of normal intellect and work for a living. The first child of the parents is a 24-year-old, clinically healthy male, who works as a basic informatics educator, teaching computer skills to the elderly. The second child is patient 2, an affected male. The mother had a brother, who – to her knowledge – was delivered by forceps, was severely mentally disabled, and lived in a special institution until he died in a fire accident at 26 years of age in the 1990s. He was nonverbal, tall statured, and had a long chin. No biological material was available.

Patient 1, an 18-year-old young woman upon the first examination, was referred to genetic counseling because of obesity, mild developmental delay, secondary amenorrhea, and minor morphological anomalies. Age at menarche was 16 years with only 1 menstruation in the following 2 years. At 16, her height was 158 cm (10th percentile), weight 109 kg (27 kg, >97th percentile), her BMI was 43.7. At 19 years, her OFC was 55 cm (50th percentile). There were striae on the skin of the lower abdomen, and acanthosis nigricans on the neck. Prader-Willi syndrome was specifically asked

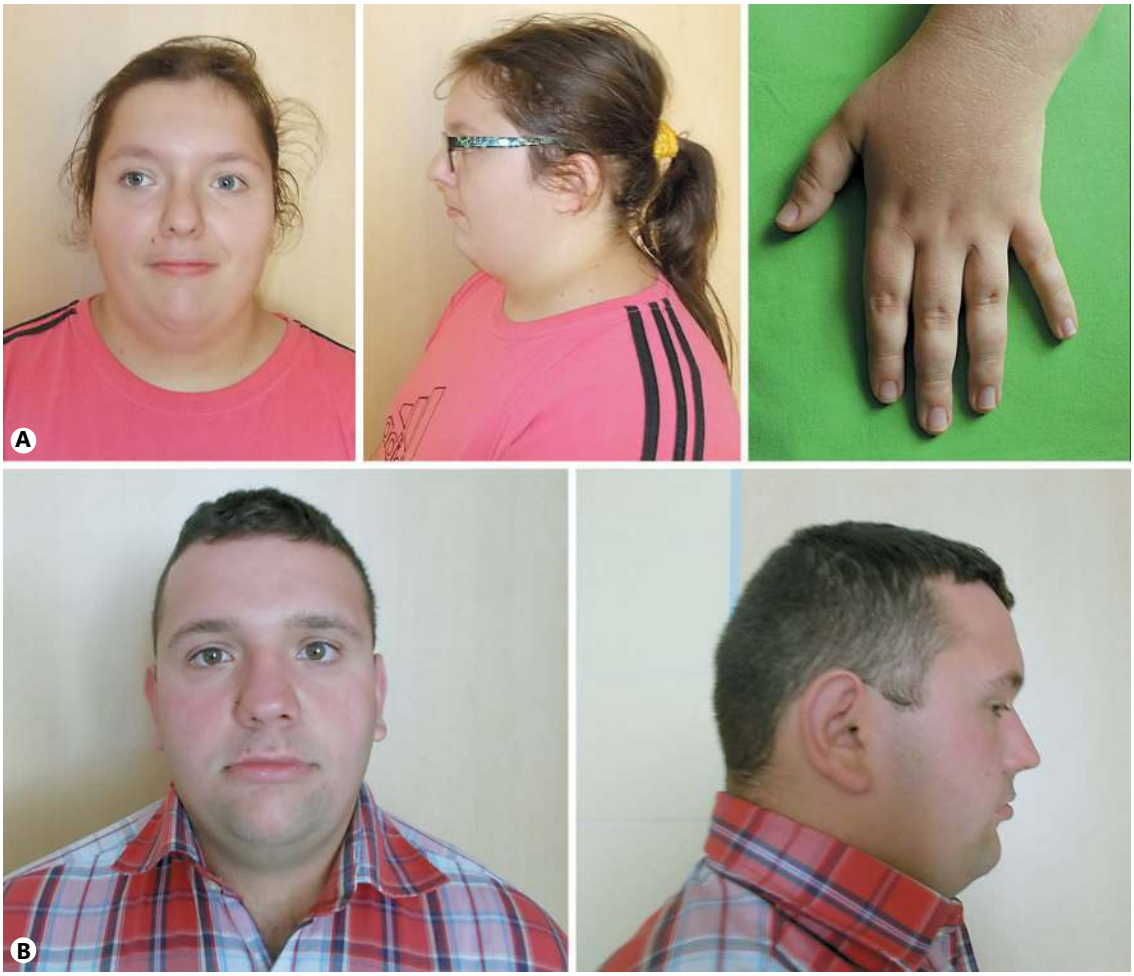

Fig. 1. A Patient 1 showing hypertelorism, divergent strabismus, broad eyebrows, high nasal bridge, bulbous tip of the nose, posteriorly low-inserted columella, small hands with tapering fingers, and an overall friendly nature. **B** Patient 2, brother of patient 1, with similar facial features. In addition, he has a deviated septum and more pronounced downslanting palpebral fissures.

to be ruled out by the endocrinologist, although the mental status and face did not resemble Prader-Willi syndrome. The patient had insulin resistance with normal fasting glucose, so dietary restrictions were prescribed. Central and peripheral sexual hormones were normal, subclinical hypothyreoidism was detected, sTSH: 8.24 mU/L (Ref: 0.3–4.2 mU/L), and corrected with L-thyroxin. Gynecological examination revealed a normal uterus and ovaries. Brain MRI was normal. Bone age was equal to chronological age.

A detailed psychological examination revealed early developmental delay – the patient achieved independent walking at 22 months – and a borderline intellect using the Wechsler Adult Intelligence Scale with uneven performance levels: verbal comprehension index was 93 (average), perceptual organization 69, processing speed 68 (both below normal), working memory 74, with a full-scale IQ of 72. She showed signs of performance anxiety, but her task awareness was above average. During the test, she replaced the more difficult, not yet automatized mathematical operations such as multiplication and division by simply adding and subtracting but came to correct results. No behavioral problems were obvious; she had a conventional, open, and friendly personality. According to the psychological evaluation, the patient compensated her learning difficulties with good verbal skills, other successful compensational strategies, and sedulity. She was able to earn a high-school degree with satisfactory grades.

Her menstruation cycle returned to normal by the age of 18 years without further medical interference.

Morphologically, the patient had hypertelorism, mildly downslanting palpebral fissures, divergent strabismus, and broad eyebrows. The nasal bridge was high, and the nose was prominent, with posteriorly low-inserted columella and a bulbous tip. She had a long philtrum and thin upper lip with downturned corners of the mouth (Fig. 1A). Her hands and feet were small, the fingers distally tapering with normal bone structure on X-ray (Fig. 1B). Table 1 shows an overview of the clinical features of the 2 patients, based on the phenotypic assessment previously used by Feenstra et al. [2006] and Magri et al. [2015].

Table 1. Overview of clinical features of our patients with distal 22q duplications

	Patient 1	Patient 2
Duplicated region	22q13.3qter	22q13.3qter
Gender	Female	Male
Age at first referral	18 years	22 years
Neurological features		
Developmental delay	Yes	Yes, noted after 3 years of age
Seizures	No	Yes, fever-associated
Intelligence	Borderline (overall IQ 76)	Borderline (overall IQ 79)
Microcephaly	No	No
Brain structural abnormality	No	No
Facial features		
Sparse, fine hair	Yes	No
Hypertelorism	Yes	Yes
Palpebral fissures	Downslanted	Downslanted
Strabism	Yes (divergent)	Yes (divergent)
Wide/high nasal bridge	Yes	Yes
Low-set ears	Yes	No
Dysplastic ears	No	No
Cleft lip/palate	No	No
Long philtrum	Yes	Yes
Retrognathia	No	No
Skeletal features		
Short neck	Yes	Yes
Short stature	No	No
Obesity	Yes	Yes
Visceral anomaly (renal, cardiac, genital)	No	No
Psychiatric problems	No	Yes
Limbs	Small hands	Normal

G-banding revealed a normal female karyotype. The facial features and the mild developmental delay raised the suspicion of DiGeorge syndrome. Therefore, 22q11.2/22q13.3 FISH was performed (DiGeorge/VCFS TUPLE1/22q13 probe mix, Cytocell, Rainbow Scientific Inc., Windsor, CT, USA). However, instead of monosomy 22q11.2, trisomy of the 22q13.3 region was detected. Analysis of metaphase chromosomes revealed that one of the chromosomes 22 contains two 22q13.3 regions, one on the short arm and one on the terminal end of the long arm (Fig. 2A). Using array CGH (Affymetrix CytoScan 750K and Affymetrix Chromosome Analysis Suite (ChAS) v2.0 Software, Affymetrix, Thermo Fisher Scientific, Waltham, MA, USA), a duplication of chromosome 22q13.31qter was identified, spanning 3,327 kb and 45 genes of which 30 are OMIM genes. *SHANK3* was encompassed in the trisomy (Fig. 2C). The exact gene content of the duplication, identical in the siblings, with OMIM numbers is as follows: *FAM19A5* (617499), *BRD1* (604589), *ZBED4* (612552), *ALG12* (607144), *CRELD2* (607171), *PIM3* (610580), *IL17REL* (613414), *MLC1* (605908), *MOV10L1* (605794), *PANX2* (608421), *SELENOO* (607917), *TUBGCP6* (610053), *HDAC10* (608544), *MAPK12* (602399), *MAPK11* (602898), *PLXNB2* (604293), *PPP6R2* (610877), *SBF1* (603560), *ADM2* (608682), *MIOX* (606774), *NCAPH2* (611230), *SCO2* (604272), *TYMP* (131222), *SYCE3* (615775), *CPT1B* (601987), *CHKB* (612395), *MAPK8IP2* (607755), *ARSA* (607574), *SHANK3* (606230), and *ACR* (102480). The patient's molecular karyotype was: arr[hg19] 22q13.3 1q13.33(47,870,362–51,197,766)×3.

Patient 2

The brother is the 2nd term-born child of the parents with a weight of 3,100 g (10th–25th percentile) and length of 50 cm (25th percentile). OFC was not recorded, but there was no suspicion of microcephaly. According to the mother's memories, he seemed to be developing normally until 3 years of age, when febrile seizures developed, reoccurring several times until the age of 5 years. On 2 occasions, the convulsions were life-threatening and required cardiopulmonary resuscitation. He received lamotrigine, later carbamazepine therapy. He was noted to be a reserved child in kindergarten, not engaging in activities with peers. Challenging behavior developed later in his school years: he often lost interest in his classes and walked out without permission, dropping into other classrooms to chat with schoolmates. He went to normal primary school but needed extra support and education to achieve his degrees. Basic grammatical, mathematical and literature skills have been acquired. Dyslexia and dysgraphia manifested in learning difficulties, but he graduated from an evening high-school with satisfactory grades. He now works as a temporary employee in a restaurant.

He was diagnosed with bipolar affective disorder, and agomelatine and aripiprazole were prescribed – the latter was omitted

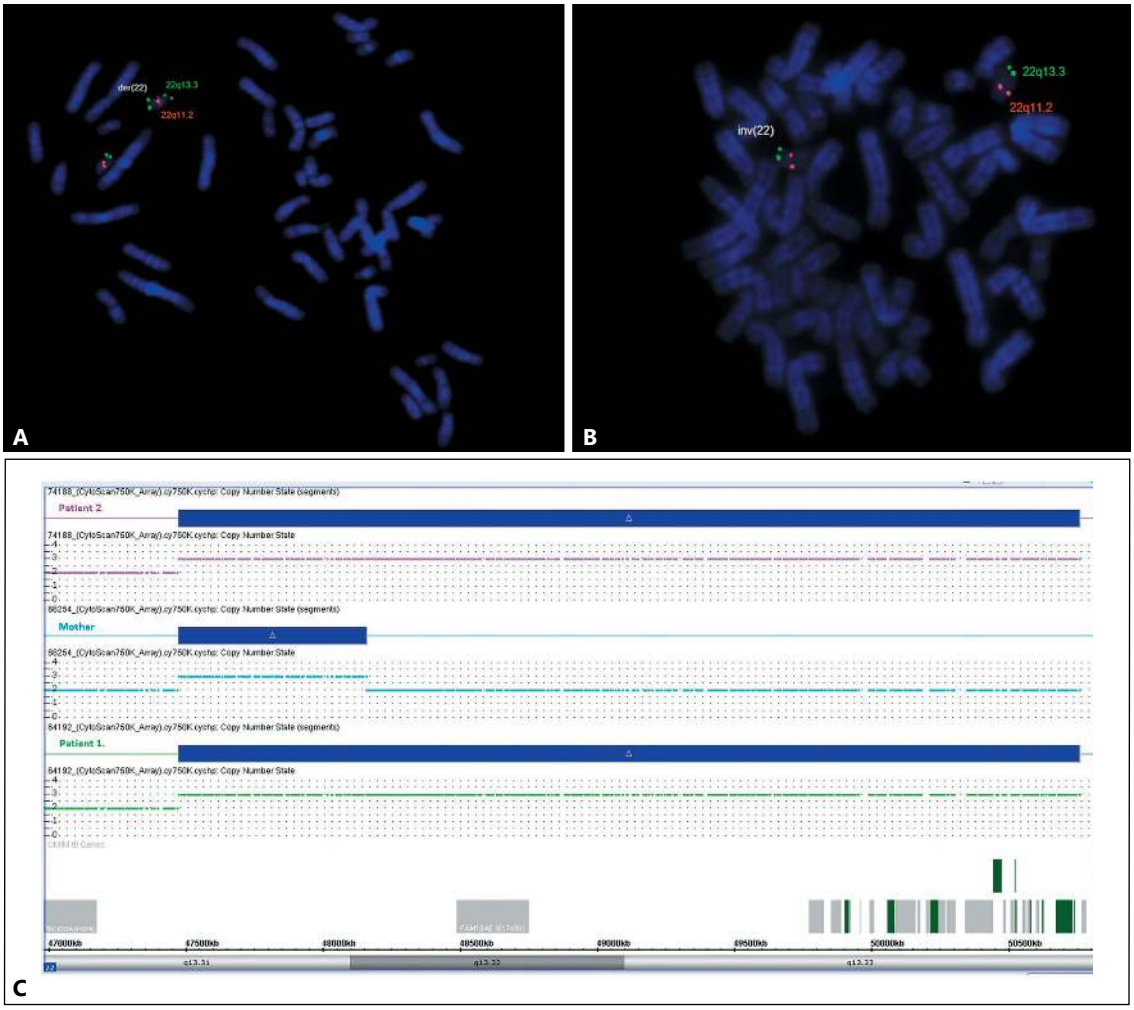

Fig. 2. A FISH on metaphase spread of patient 1 using locus specific probe for 22q11.2 (TUPLE1; red) and 22q13.3 (N85A3; green). The latter covers the telomeric end of the *SHANK3* gene, allowing the identification of the most distal 22q13.3 rearrangements. The abnormal chromosome 22 contains two 22q13.3 signals. **B** FISH on metaphase spread of the mother using locus specific probe for 22q11.2 (TUPLE1; red) and 22q13.3 (N85A3; green). The inv(22) shows the inverted chromosome 22 and relocation of the 22q13.3 region to the short arm. **C** Array CGH of the probands and the mother using Affymetrix 750K platform. The analysis shows the identical duplication (blue bars) of 3,327 kb involving the 22q13.31q13.33 region in patient 1 and 2, with the breakpoints falling between 47,870,362 and 51,197,766. The smaller duplication detected in the mother's sample (middle) contains no OMIM genes. Dashed lines represent copy number statuses.

because of fatigue, which he attributed to his medication. He has mild sleep disturbance, low frustration tolerance and occasional temper tantrums. Apart from this, he still likes to play with toys that are inappropriate to his age and comprehension, such as toy cars and tying knots on strings. His overall IQ at 18 years of age was 79; verbal IQ was 81, and performance 79. His head circumference was 59 cm (90th percentile).

Cytogenetic analysis of peripheral blood showed a normal male karyotype. FISH study with a DiGeorge-specific probe mix confirmed the trisomy of the 22q13.3 region with the same signal pattern as in his sister. Array CGH was also performed; the breakpoints and the size of the duplicated 22q13.3 region were identical to his sister's duplication (Fig. 2C). Parental FISH testing clearly revealed a pericentric inversion of chromosome 22 with breakpoints 22p13 and 22q13 in the mother with the following karyotype: 46,XX.ish inv(22)(p13q13.3)(p13)(N85A3+)(q13.3)(N85A3–) (Fig. 2B). Based on the mother's FISH result, the final karyotypes of the probands were: 46,XX.ish rec(22)dup(22q13.3)inv(22)(p13q13)mat and 46,XY.ish rec(22)dup(22q13.3)inv(22)(p13q13)mat. Array CGH performed on the mother's DNA sample showed a small duplication (685 kb, breakpoints 47,474,613 and 48,159,741) at the proximal breakpoint of the duplicated region detected in the probands (Fig. 2C). Presumably, this segment was duplicated as part of the process that generated the inversion.

Based on the gene content (no OMIM genes) and the literature data, this duplication does not have phenotypic consequences.

The healthy male sibling's FISH testing revealed a normal signal pattern; he was not a carrier of a pericentric inversion either.

Discussion

Pure duplications of chromosome 22q, without concomitant aneusomies of other chromosomes, are exceedingly rare. Underreporting of mild cases may create a selective bias, so the true incidence of the condition remains unknown. Array CGH is a powerful tool in identifying causal copy number changes in patients with intellectual disability; it is considered to be useful even in cases of mild mental retardation [Liang et al., 2008; Coutton et al., 2015].

Most of the reported distal 22q trisomy cases were extensively studied, and the clinical features were overviewed in details by Feenstra et al. [2006] and Magri et al. [2015], latter focusing on duplications distal from 22q13. The cases described by Pramparo et al. [2008], Shimojima et al. [2009], Samanich et al. [2012], and Rahikkala et al. [2013] should be handled separately – their patients having small interstitial duplications more proximally (22q13.1 to q13.31), with overall more severe phenotypes. The frequency of pericentric inversions, excluding the common/polymorphic inversions, is estimated to be 0.12–0.7% [Gardner et al., 2011]. According to Koolen et al. [2005] the presence of recurrent proximal breakpoints at 22q13 indicates that these specific regions are prone to recombination that may lead to translocations, inversions, duplications, and deletions. Pericentric inversions are balanced rearrangements without phenotypic consequence; however, through recombination between the normal and the inverted allele, a parent with an inversion may transmit an unbalanced, rearranged form of the inverted chromosome to the offspring.

In this study, we reported the familial recurrence of terminal 22q duplication with 2 affected siblings originating from maternal pericentric inversion in chromosome 22 (p13q13.3). The breakpoints and the size of the detected duplication were identical in patient 1 and patient 2, suggesting the same sequence and course of recombination events between the inverted and the normal maternal homologue of chromosome 22. The small duplication found at the breakpoint of 22q13.3 in the maternal chromosome 22, partially overlapping with the proximal breakpoints of the 22q duplication in her children, is likely the result of recombination within the inversion loop.

Peeters et al. [2008] found evidence for a consistent clinical presentation in 22qter duplication: mild to moderate mental retardation, microcephaly, and similar mild dysmorphic features. Indeed, an overview of the cases in the literature, except for those published by Schinzel [1981], Jafri et al. [2011], and Han et al. [2013], report microcephaly. In our report, both patient 1 and 2 have mild dysmorphic features, such as hypertelorism, divergent strabismus, high nasal bridge, and a bulbous nose tip; they both developed obesity and learning difficulties. Yet, unlike most patients with distal terminal duplications, they both have normal height and head circumference, and borderline intellect, albeit with the help of long-term therapies. The phenotype seems milder in the young woman than in her brother, as she has no behavioral or adaptive problems. In their recent paper, Han et al. [2013] pointed out features that are the consequence of *SHANK3* overexpression: hyperphagia, seizures, reduced social interactions, and manic-like behavior. They reported 2 patients with the smallest duplications so far, yet the neurobehavioral and psychiatric symptoms were quite prominent. In our case, obesity in both patients and the neuropsychiatric symptoms of patient 2 – maladaptive behavior, epilepsy, repetitive monotonous playing, and bipolar affective disorder – are highly reminiscent of features reported by Han et al. [2013]. Epilepsy as a clinical consequence of *SHANK3* overexpression was also reported by Jin et al. [2018]. We assume that a gene dosage effect originating from the duplication of *SHANK3* in our patients is responsible for the overlapping phenotype, yet recent literature points out the modifying effect of post-transcriptional regulation of the *SHANK3* expression [Choi et al., 2015].

In conclusion, our report supports the observation of previous authors that clinical features in the 22qter duplication syndromes show great variability, and the size of the duplicated segment does not always correlate with the phenotypic severity. Our patients are 2 of the very few published cases of familial recurrence of 22qter duplication syndrome characterized by array CGH, and they represent unusually mild phenotypes without microcephaly, yet with detectable neuropsychiatric symptoms in one of them.

Statement of Ethics

Written informed consent for genetic testing and publication of photo material was obtained from all individuals. Although the tests were performed on a diagnostic purpose, ethical approval was also obtained (28676-7/2017/EÜIG).

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contribution

Katalin Szakszon and Anikó Ujfalusi prepared the manuscript. Anikó Ujfalusi supervised the molecular cytogenetic studies of the patients. Katalin Szakszon is also the clinical geneticist who performed clinical assessment, examination, and genetic counseling of the family. Orsolya Nagy and Beáta Bessenyei performed molecular karyotyping and cytogenetic studies. Ádám Borbély was the psychiatrist of patient 2, and Györgyi Lente was the psychologist of patient 1; they assessed the behavioral and intellectual characteristics. Irén Kántor was the endocrinologist who also raised the suspicion of a possible genetic cause of the symptoms. All authors took part in revising the relevant sections.

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